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Vitamin D in chronic kidney disease: is the jury in?

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Vitamin D shows promise for improving diverse health outcomes among patients with chronic kidney disease. Observational studies of vitamin D medications have contributed important evidence for broad beneficial clinical effects of vitamin D beyond actions on bone. However, such studies are limited by the potential for confounding by indication. A large randomized controlled trial is now needed to test the hypothesis that vitamin D therapy improves clinical outcomes in patients with kidney disease.

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Vitamin D products have been used for nearly three decades to treat secondary hyperparathyroidism in patients with chronic kidney disease (CKD). Although bone health continues to be the primary motivation for prescribing vitamin D (cholecalciferol, ergocalciferol, calcitriol, and activated vitamin D analogues), interest in the pleiotropic actions of vitamin D has recently taken center stage.[1] Vitamin D receptors are present throughout the body in diverse tissues, and hundreds of human genes contain vitamin D response elements. Evidence for potential beneficial effects of vitamin D on immune function, cancer, and cardiovascular disease derives from experimental and animal models, associations of circulating vitamin D levels with health outcomes, nutritional epidemiology, and ecological studies.

Pharmacoepidemiology studies— observational studies of medications— contribute additional evidence for broad beneficial clinical effects of vitamin D beyond actions on bone. Three large such studies have reported an approximately 20% lower risk of death among chronic hemodialysis patients treated with intravenous calcitriol or its analogues.[2–4] Two smaller studies have observed 26% and 65% lower mortality risks among predialysis CKD patients treated with oral calcitriol.[5,6] Pharmacoepidemiology studies are more expedient and less expensive to conduct than randomized controlled trials (RCTs), and they provide additional opportunities to assess medication use in real-world settings. They often include individuals with multiple comorbid illnesses, who may be excluded from RCTs, and provide adequate follow-up time to evaluate clinically relevant end points and detect rare adverse effects.[7]

Naves-Díaz *et al.*[8] (this issue) present results of a new pharmacoepidemiology study of vitamin D. The authors studied 16,004 hemodialysis patients from six Latin American countries for a median of 16 months. They found oral calcitriol use to be associated with a 45% reduction in relative risk for mortality. Similar beneficial associations were observed for deaths due to cancer, infection, and cardiovascular disease, which were ascertained with International Classification of Disease-10 codes. Importantly, the association of calcitriol use with survival was independent of circulating parathyroid hormone (PTH) concentrations. This finding is consistent with prior studies[2,5,6,9] and suggests that targeting vitamin D therapy to PTH may not be the most effective treatment strategy. Novel aspects of the study by Naves-Díaz *et al.*[8] include a Latin American patient population, which may differ in terms of genetics, lifestyle factors, and practice patterns as compared with North American patients; assessment of mortality due to diverse causes; and evaluation in a hemodialysis population of oral calcitriol, which is widely available and relatively inexpensive.

However, pharmacoepidemiology studies have an important limitation: the potential for confounding by indication. Patients and their physicians make individualized decisions to initiate medications. These decisions often incorporate subtle aspects of health and health care that are not readily evident from information available in most studies. Confounding by indication occurs when the characteristics of study subjects who receive a specific medication differ systematically from the characteristics of those who do not, and these differences, rather than the medication itself, affect clinical outcomes. Modern pharmacoepidemiology studies use many techniques that attempt to simulate an RCT and achieve a fair comparison of medication users with non-users. These techniques include restricting the study population to subjects with an indication for the drug of interest; studying incident (new) medication users to capture early events that may occur after initiation of therapy; accurately ascertaining medication use, subject characteristics, and primary outcomes; and analyzing subjects according to their initial medication use.[7]

Naves-Díaz *et al.*[8] make laudable efforts to minimize confounding by indication. Nonetheless, available data limit their ability to comprehensively address this potential limitation. First, 'baseline' participant characteristics were obtained from initial study enrollment and may not accurately reflect current health status at the time of calcitriol initiation. Second, the available data sources do not permit precise ascertainment of comorbid conditions and socioeconomic status. Third, prevalent and incident calcitriol users were combined, potentially obscuring early effects of calcitriol. Finally, a non-trivial proportion of study subjects (11%) were censored for reasons that may introduce bias (for example, transplantation, change in renal

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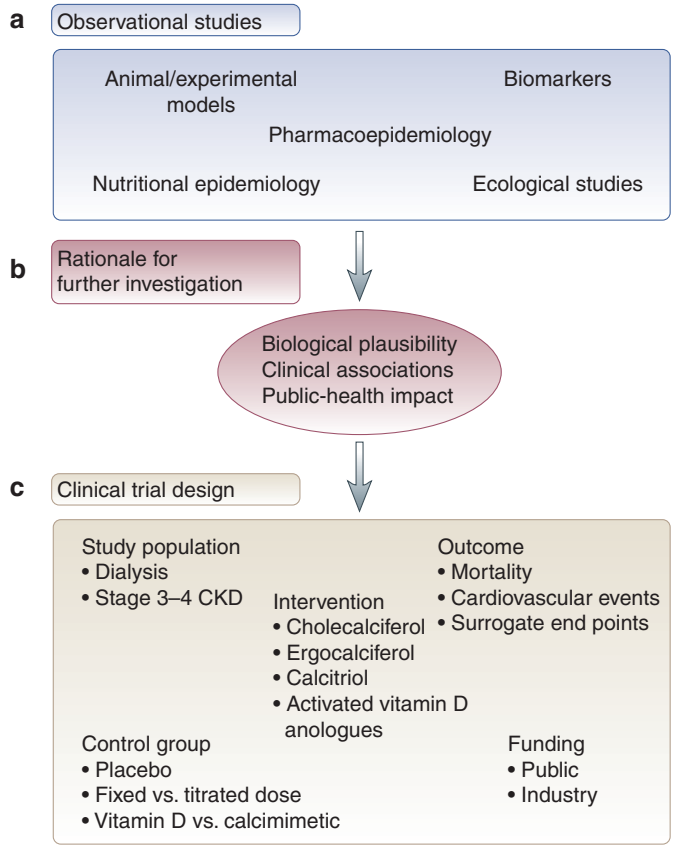

Figure 1 | Reseach on Vitamin D in chronic kidney disease. Observational studies (**a**) have developed a strong rationale for further investigating the clinical effects of vitamin D in chronic kidney disease (**b**). A large randomized clinical trial is needed to test whether vitamin D truly improves health outcomes. Such a trial faces unique design challenges (**c**).

replacement modality, withdrawal from dialysis, or recovery of renal function). One must question whether the observed 45% reduction in mortality, which is larger than most previous studies report[2–5] and may appear 'too good to be true,' reflects, in part, residual confounding.

What are we to conclude? Observational studies may refine our understanding of vitamin D but cannot provide definitive evidence of clinical benefit. Instead, a well-designed RCT of vitamin D in CKD is needed to address whether vitamin D affects clinical health outcomes in this patient population (Figure 1). RCTs overcome many potential biases of observational studies and are the gold standard for evaluating the clinical effectiveness of medical interventions. Historical comparisons encourage humility: observational data, supported by biologic plausibility, strongly suggested that estrogen replacement therapy and vitamin E each prevented cardiovascular disease, but RCTs demonstrated a lack of benefit or even harm from these interventions.

An RCT of vitamin D in CKD is justified because large potential benefits (survival) and costs (pharmaceutical expenditures) are at stake, and because we remain in a state of equipoise. The sum of existing data suggests that vitamin D treatment may improve survival in CKD, but these data are neither conclusive nor sufficient to determine optimal clinical care. Additional studies that examine intermediate end points, such as change in cardiovascular risk factors or immune function, may be useful by providing biologic plausibility to support the associations described in observational studies. However, because vitamin D may have diverse effects on many organs, beneficial effects on one biologic end point may counterbalance adverse effects elsewhere, or vice versa. Only a large trial examining broad clinical end points such as mortality or cardiovascular events can capture the full clinical impact of vitamin D treatment.

A number of unique issues make design of a successful trial of vitamin D in CKD particularly challenging. First is the choice of study population(s). The hemodialysis population is attractive because it is readily identifiable for recruiting; therapy can be directly administered during treatment sessions, reducing potential for nonadherence; and hemodialysis patients experience an unacceptably high mortality rate, both motivating definition of optimal interventions and decreasing the sample size necessary for a clinical trial. However, the hemodialysis population is complex because of highly prevalent use of calcitriol, paricalcitol, various phosphate binders, and calcimimetics. In addition, existing guidelines specify that treatments be directed to PTH, despite a lack of compelling evidence that this approach improves clinical outcomes. These issues may be minimized by targeting of incident hemodialysis patients. Alternatively, an RCT could target stage 3–4 CKD. Stage 3–4 CKD affects many more people than end-stage renal disease, the use of medications affecting mineral metabolism is currently less common in this population, and two studies suggest that the relative effects of vitamin D on mortality are similar to those observed in end-stage renal disease.[5,6]

Second, multiple potential interventions exist. Calcitriol and its analogues have differential effects in various tissues. However, the exact mechanisms through which vitamin D may reduce mortality are not known; this precludes confident selection of a single superior vitamin D agent. In addition, there is increasing interest in potential paracrine and/or autocrine effects of vitamin D,[1] which may be best activated by administration of a substrate form of vitamin D (cholecalciferol or ergocalciferol). Cholecalciferol or ergocalciferol could be given in combination with an activated form of vitamin D or could be tested in a separate treatment arm.

Third, control interventions will be controversial. A placebo control would optimize identification of any vitamin D effect, but higher PTH levels in a placebo group may generate ethical concerns and/or differential use of other medications to lower PTH. Alternative designs to a placebo control, such as fixed vitamin D dose versus vitamin D titrated to PTH, or vitamin D

versus calcimimetic, will not directly test the scientific question at hand. These issues will be particularly relevant if the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events trial demonstrates an effect of cinacalcet on mortality.[10]

Finally, RCTs are expensive. The design issues outlined above are subtle and complex, with potential for conflicts between patient benefits and corporate marketing strategies. Public funding will be required to ensure that trial results maximally benefit patients.

Diverse and creative research by the nephrology community has generated renewed interest in vitamin D. We are currently challenged with the task of translating exciting discovery into improved clinical care for our patients. Pharmacoepidemiology studies have added critical data regarding the potential beneficial effects of vitamin D therapy in CKD. A large RCT is now needed to test the hypothesis that vitamin D therapy improves clinical outcomes in patients with kidney disease.

DISCLOSURE
The authors declared no competing interests.

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The hunt for the perfect biomarker for acute kidney injury: back to gamma-trace?

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The hunt for a good biomarker for acute kidney injury (AKI) is currently hot. It has recently been the subject of several excellent reviews[1–3] and a useful meta-analysis,[4] and we are hearing exhortations that this hunt should get high priority.[3,5] The ideal marker (or set of markers) should facilitate early identification, stratify risk, and contribute to informative diagnostic classification. Perhaps most importantly, a good marker should aid the testing of interventions to prevent development of AKI and improve management. So, there are very good reasons to get on with it!

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While the practical arguments are persuasive, a secondary benefit of acute kidney injury (AKI) biomarker research will also be new basic understanding. An intriguing example is the recent paper by Ichimura and co-workers on KIM-1, one of the current candidate AKI biomarkers.[6] In a study published in May 2008 in the *Journal of Clinical Investigation*, these investigators show that injured proximal tubule cells develop phagocytic capacity and become macrophage-like in their behavior. KIM-1, an epithelial cell surface protein upregulated by injury and shed into the urine by damaged cells, appears to play a causal role in this transformation. The finding that epithelial cells can acquire a phagocytic phenotype is unexpected and potentially important for tissue repair and recovery.

In this issue of *Kidney International*, Koyner and co-workers[7] report data on another current candidate, urinary cystatin C. This study also raises biological questions and reminds us that that there are important unanswered questions about the renal biology of cystatin C. Cystatin C has a curious history. Serum cystatin C is getting all the attention these days for its potential utility for the estimation of glomerular filtration rate. But cystatin C was actually first identified not as a serum marker but as a urinary marker. In 1961 Frederick Flynn, a clinical pathologist at University College Hospital, and Elizabeth Butler, a nurse at the same institution, reported a novel protein in urine of patients with proteinuria, which they called post-gamma protein because of its position after γ-globulins on an electrophoretic gel.[8] In the 'biomarker' literature of that period, gamma-trace, as it came to be called, was placed in the group of low–molecular weight proteins associated with 'tubular' injury, hence part of 'tubular' proteinuria. Flynn and Platt argued that the presence of small proteins such as gamma-trace in urine reflected a failure of proximal reabsorption of freely filterable proteins,[9] a question still of interest and still in need of further study.

The next chapter in the gamma-trace/cystatin C story takes place in Sweden about 20 years later. The key investigators were two clinical pathologists at the University of Lund in Sweden, Anders Grubb and Helge Löfberg. They pursued

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